

Supplementary Materials for

Paying for innovation: Reimbursement incentives for antibiotics

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Methods

To characterize market trends of new antibiotics from 1990 to 2012, we created a database merging historical product-by-product sales data from EvaluatePharma (Evaluate Group Ltd., London, UK) with information from company annual reports, regulatory filings (with the U.S. Securities and Exchange Commission), and equity research reports. In addition to antibiotics, we also examined marketed cardiovascular (39, 25%) and cancer and immunotherapy (59, 46%) drugs, which have been the focus of considerable pharmaceutical company interest, resulting in our study dataset of 127 marketed products. We focused on sales for branded drugs, which refer to those created and marketed by inventor companies. Our dataset excluded an unknown number of drugs which had annual sales of less than \$1 million annually. However, when companies assess the market potential of investigational products, they base their estimates on the commercial performance of successful products, representing the peak potential market size of their compound, adjusted for the risks of failure before approval.

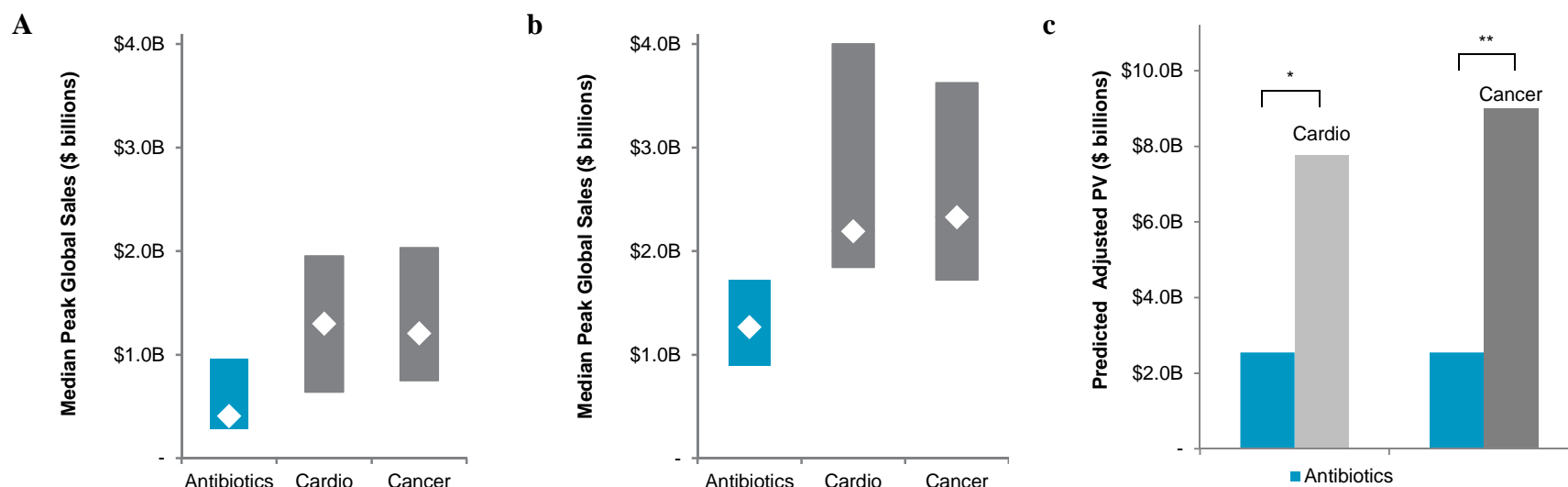
One commonly used metric of a drug's profitability is its peak sales, defined as the highest recorded annual sales worldwide, and a drug grossing peak sales of a billion dollars or more is generally considered a blockbuster. Among marketed products, median peak global sales for antibiotics were \$407 million (interquartile range [IQR]: 280-959) in constant 2012 dollars, compared with \$1,205 million (IQR: 750-2,031) for cancer drugs and \$1,299 million (IQR: 638-1,952) for cardiovascular drugs (Figure 1a). Similarly, when considering only the top twenty best-selling products in each therapeutic area, peak sales for antibiotics were significantly lower than those for cardiovascular and cancer drugs (Figure 1b).

Given that newly approved drugs can be cash-generative for up to a decade or more depending on the timing of entry of generic competitors, we also evaluated the present value of revenues for the drugs in our dataset. Present values (PV) appropriately account for the time value of money, a core tenet of modern finance theory, which holds that future wealth must be adjusted or "discounted" for the possibility of interest earned or inflation accrued in the intervening period. We used a discount factor of 10%, which is standard in pharmaceutical economic models. Median PVs between pairs of therapeutic areas relative to antibiotics (*i.e.*, antibiotic vs. cancer, antibiotic vs. cardiovascular) were compared using the nonparametric Wilcoxon signed-rank test. The ANCOVA test was used to assess the statistical significance of differences across all groups.

After controlling for the number of patent-protected years of marketing, year of patent expiry, firm location, and firm size in multivariable regression models, we found that the median PV of antibiotic sales remained significantly lower than that of cancer and cardiovascular drugs (ANCOVA test between groups, $P < 0.001$). To illustrate this difference, we derived the median predicted PV of antibiotics and cancer and cardiovascular drugs assuming ten years of patent protection after regulatory approval (Figure 1c). Restricting antibiotics to systemic antibacterials only had no effect on these comparisons.

All historical sales were adjusted for inflation using the average of inflation estimates from the U.S. Office of Management and Budget and the Congressional Budget Office. Data (in Figures S1 and S2) are presented in constant 2012 dollars. Statistical analyses were conducted with Stata v. 12.0 (StataCorp), and two-tailed P values less than 0.05 were considered significant.

Fig. S1. Median peak and present value of global sales of antibiotic, cancer, and cardiovascular drugs from 1990 to 2012.



Notes: * $p < 0.05$, ** $p < 0.01$. (a) Median peak global sales of antibiotic, cardiovascular, and cancer drugs. Diamonds represent median values; shaded grey bars are interquartile ranges (IQR). (b) Median peak global sales for the top twenty antibiotic, cardiovascular, and cancer drugs by gross peak sales. (c) Predicted adjusted present value (PV) of sales based on multivariable regression analysis assuming ten remaining years of patent protection and controlling for year of patent expiry, firm location, and firm size. There were significant differences in PV between the three groups (ANCOVA test, $p < 0.001$).

Fig. S2. Cumulative global sales of selected branded antibiotics.

